

Exhibit 8

Distribution of donor lungs in the United States: a case for broader geographic sharing

Iribarne A, Meltzer DO, Chauhan D, Sonett JR, Gibbons RD, Vigneswaran W, Russo MJ. Distribution of donor lungs in the United States: a case for broader geographic sharing.

Abstract: Objectives: To evaluate the association between allocation of donor lungs by geographic sharing type (GST) and lung allocation score (LAS).

Methods: UNOS data included lung transplant recipients between 5/4/05 and 09/30/15 ($n = 17\,416$) grouped by GST of donor lungs: local, regional, or national. Recipients were stratified by LAS <50, 50–75, and >75. Kaplan–Meier analysis was used to assess five-yr survival.

Results: The majority of lungs were shared locally ($n = 9200$; 52.8%) followed by nationally ($n = 5356$; 30.8%) and regionally ($n = 2860$; 16.4%). There was a significant difference in the mean LAS at transplant (local: 43.7 ± 15 ; regional: 49.5 ± 18.8 ; national 51 ± 19.4 ; $p < 0.001$). There was a significant association between GST and LAS ($p < 0.001$). The majority ($n = 7431$; 58.2%) of recipients with LAS <50 received local lungs. Recipients with LAS >75 received a majority of their organs from national ($n = 881$; 45.4%) and regional ($n = 414$; 21.6%) donors. Although statistically significant ($p = 0.024$), absolute decline in five-yr survival by GST in the national GST was only 1.1% compared to the local GST.

Conclusions: Nearly half of all lungs in the United States are allocated locally to recipients with an LAS <50. Additional studies should determine if organ sharing over broader geographies would improve waitlist outcomes.

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Key words: donor lung – geographical distribution – lung allocation score – lung transplant – United States

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Conflicts of interest: None.

Accepted for publication 8 March 2016

Current organ procurement, allocation, and transplantation practices in the United States, are complex and based on geographic boundaries defined by the United Network for Organ Sharing (UNOS). Organ allocation can be local, regional, or national. In most instances, the local unit is the Organ Procurement Organization (OPO) in that area. The OPO is accepted as a member of UNOS and is authorized by the Health Care Financing Administration (HCFA) to procure organs for transplantation. For each OPO, the HCFA defines a geographic procurement territory within which the OPO concentrates its efforts. This territory usually encompasses several miles from the organ pro-

curement hospital. A region, on the other hand, comprises four or five states including and around the state in which the organ is procured. Currently, the United States is divided in 11 geographic regions to facilitate organ transplantation. If there is no suitable recipient for the donor, the organ is allocated beyond regions and can be allocated nationally, meaning anywhere in the United States. (1)

Given the disparity between potential recipients and available donors, efficient methods of organ allocation are needed to achieve maximal benefit from existing organs. In an effort to reduce waitlist mortality, the Organ Procurement and Transplantation Network (OPTN) Lung Allocation Subcommit-

tee recommended two significant changes in lung allocation policies in 1998: (i) to allocate organs based on medical urgency and (ii) to minimize the effects of geography on waitlist outcome (2).

In response to the Subcommittee's request, the Lung Allocation Score (LAS) was implemented in May 2005 to allocate organs based on predicted net survival benefit of transplantation. The LAS is calculated based on a multivariable model that is a weighted combination of predicted survival on the waitlist for one yr and predicted post-transplant survival at one yr (3). Since the introduction of the LAS, favorable trends in waitlist times and waitlist mortality have been observed (4–7). However, findings from our group suggest that even within the LAS-era, a high proportion of organs are being allocated to low-priority candidates, while candidates with a higher LAS continue to die at high rates on the waitlist (8).

These observed inefficiencies in organ sharing may be in part due to the locally based allocation structure. The importance of geography on waitlist outcomes in transplantation has been well recognized (1). Under the current “local” lung allocation system, available organs are initially offered only to the subset of appropriately matched transplant candidates (based on blood group and size) within the donor's local geographic unit, known as the donor service area (DSA). If an available organ is first accepted for a candidate within the local DSA, it is never offered to potentially more severely ill candidates at the broader regional or national level, even if the non-local candidate has a higher LAS. The purpose of this study was to describe the allocation of donor lungs by geographic sharing type (GST) (local, regional, or national) and LAS at time of transplant.

Materials and methods

Data collection

The Standard Transplant Analysis and Research Dataset was provided by UNOS (data source #010311-3). The dataset contains information collected from the UNetSM database forms, including the Transplant Candidate Registration form, the Transplant Recipient Registration form, and the Transplant Recipient Follow-up form. These data are the basis for the UNOS Thoracic Registry.

Study population

UNOS provided de-identified patient-level data for all lung transplant candidates and recipients in the United States. Use of these data is consistent with

the regulations of our university's institutional review board and the UNOS Data Use Agreement. The analysis included lung transplant recipients aged ≥ 12 yr old and listed between May 4, 2005 and September 30, 2015 ($n = 17\,416$). Follow-up data were provided through December 3, 2015. Patients were followed from the date of listing until death, transplantation, re-transplantation, or date of last known follow-up provided by UNOS. Recipients who underwent simultaneous transplantation of another organ ($n = 91$) and those with missing LAS data ($n = 432$) were excluded from the analysis.

To study the effect of geography on waitlist outcomes, GST was categorized using data supplied by UNOS as: local (within the OPO), regional (outside of the OPO, but within the same sharing region), or national (outside of the sharing region). Patients were also stratified into three groups based on LAS at the time of transplant. The categorization of LAS was based on previously defined LAS thresholds (8, 9): <50 (“low priority”), $50\text{--}75$ (“intermediate priority”), >75 (“high priority”).

Data analysis

All data were analyzed using the statistical software package, Stata 14 (Stata Corp, College Station, TX, USA). Continuous variables were reported as means and categorical variables reported as frequencies. Continuous variables were compared using the Student's *t*-test, while categorical variables were compared using the chi-square test. The analysis of variance (ANOVA) test was utilized to compare means between GST and LAS categories. The univariate log-rank test for equality of survivor functions was used for survival analysis. The conventional *p*-value of 0.05 or less was used to determine the level of statistical significance. All reported *p*-values are two-sided.

The primary analysis reports the distribution of donor lungs by GST and LAS category. The secondary analysis examines post-transplant graft survival by GST. For post-transplant graft survival, recipients were followed from date of transplant to graft failure (defined by patient death or re-transplantation) or last known follow-up. The outcome of interest was graft loss. Candidates were censored as either lost or alive at last known follow-up.

Results

Patient characteristics

From May 4, 2005 to September 30, 2015, there was a total of 17 421 lung transplant recipients in

Iribarne et al.

the United States. The GST was distributed as follows: local, $n = 9200$; regional, $n = 2860$; and national, $n = 5356$. Five organs were transplanted outside the United States, and they were excluded. Baseline characteristics of the three groups, in addition to select recipient characteristics, are shown in Table 1.

Geographic distribution of organs

The distribution of donor lungs by GST and recipient LAS category is shown in Fig. 1. Using the ANOVA test, we found that there was a significant association between broader geographic sharing and higher LAS at the time of transplant ($p < 0.001$). While 80.77% ($n = 7431$) of local organs were allocated to recipients with LAS <50 , this proportion decreased to 63.77% ($n = 3416$) for national donors. Conversely, 7% ($n = 644$) of local organs were allocated to recipients with LAS >75 , but this proportion increased to 16.45% ($n = 881$) for national donors. There was a significant difference in the mean LAS at the time of transplant between the three GSTs (local: 43.7 ± 15 ; regional: 49.5 ± 18.8 ; national 51 ± 19.4 ; $p < 0.001$), with the highest mean LAS in the national sharing group and the lowest mean LAS in the local sharing group.

Outcomes by geographic region

Post-transplant survival stratified by GST is shown in Fig. 2. The difference in survival across GST approached statistical significance ($p = 0.024$). At 90 d, survival rates for local, regional, and national groups were 93.8%, 93.6%, and 92.7%, respectively. At one yr, survival rates for local, regional, and national groups were 85.7%, 84.7%, and 83.8%; at five yr 54.2%, 51.6%, and 53.1%; and at 10 yr 27.1%, 27.5%, and 29.6%, respectively. At five yr post-transplantation, there was only a 1.1% difference in survival between local and national groups.

Discussion

The results of this analysis demonstrate that within the locally based lung allocation system, close to half of donor lungs go to patients with an LAS <50 and, in instances of broader geographical sharing, that proportion decreases. These observations highlight two potential shortcomings of the current allocation system: (i) low-priority patients may be receiving a disproportional share of donor organs and (ii) geography may have a significant influence on waitlist outcomes.

Instances where low-priority patients (i.e., LAS <50) are being transplanted over high-priority patients (i.e., LAS >75), potentially on the basis of geography, are concerning because low-priority patients receive little or no net survival benefit from transplantation (8). While patients with LAS <50 have a mean survival in the absence of transplantation measured in years, patients with LAS >75 have a mean survival in the absence of transplantation measured in days. Annually, hundreds of lung transplant candidates die on the waitlist, with more than 60% of them being high-priority candidates (8), despite high-priority candidates representing less than 10% of all candidates listed for lung transplantation (8). The results of our analysis show that broader geographic allocation of donor lungs may result in an increase in the proportion of high-priority candidates being transplanted.

Local allocation does more to influence transplantation outcomes than increase the proportion of low-priority recipients. There are also substantial disparities in both the structure and clinical outcomes of donor service areas (DSAs), the local allocation region. DSAs vary in size from a few counties to multi-state complexes (10). The total population served by each DSA varies more than 10-fold, from approximately 1 300 000–18 700 000 people. Further, each DSA is overseen by an independent managing organization, known as an OPO. Each OPO has different policies and

Table 1. Baseline characteristics stratified by geographic region

Baseline variable	Local N = 9195	Regional N = 2860	National N = 5356	p-Value
Donor age in years (mean \pm SD)	33.33 \pm 13.8	34.75 \pm 14.5	35.19 \pm 15.0	<0.001
Ischemic time in hours (mean \pm SD)	4.6 \pm 1.6	5.3 \pm 1.6	6 \pm 1.7	<0.001
Donor IDDM	549 (6%)	192 (6.7%)	411 (7.7%)	<0.001
Donor pulmonary infection	4672 (50.8%)	1428 (49.9%)	2502 (46.7%)	<0.001
Recipient on ECMO	148 (1.6%)	94 (3.3%)	211 (3.9%)	<0.001
Recipient intubated	432 (4.9%)	245 (9.4%)	563 (11.7%)	<0.001

ECMO, extracorporeal membrane oxygenation; IDDM, insulin-dependent diabetes mellitus.

Distribution donor lungs geography

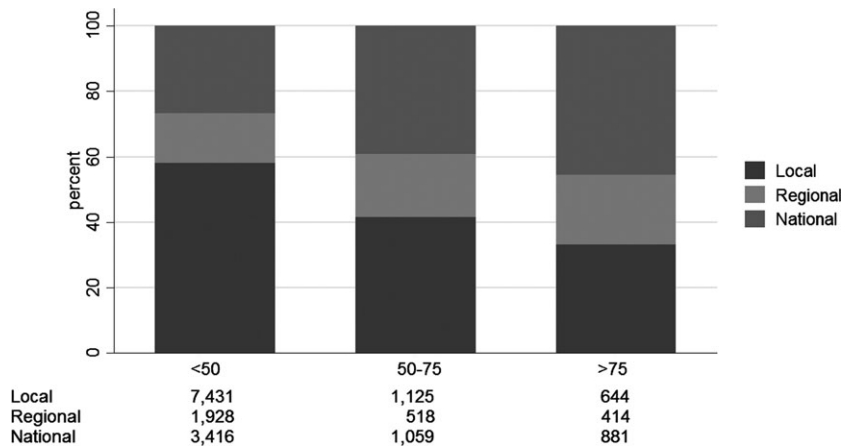


Fig. 1. Distribution of donor lungs by geographic region and lung allocation score category of recipient.

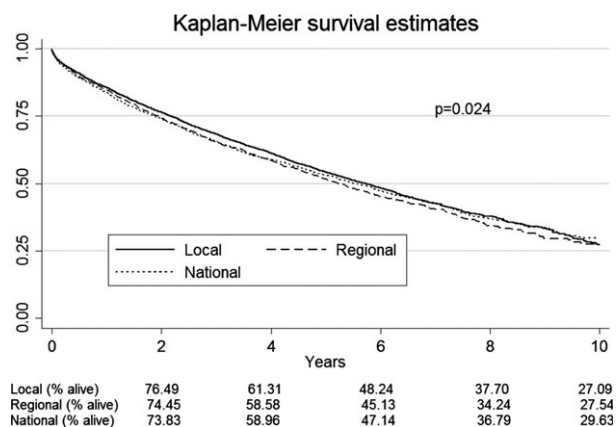


Fig. 2. Post-transplant survival stratified by geographic region of donor organ.

practices to accommodate local preferences, contributing to significant procedural and performance measure variation across OPOs (11): the number of eligible donors reported, total donors recovered, and the total number of organs transplanted vary from 15- to 25-fold. This dramatic variability translates into disparities in outcomes for transplant candidates depending on where they reside.

A common argument made against broader organ sharing is that longer ischemic times will lead to lower post-transplant survival. However, this was not observed in our analysis. As demonstrated in Fig. 2, there was no clinically significant difference in survival when stratified by GST. For example, at five yr post-transplantation there was only a 1.1% difference in survival between local and national groups. This finding was observed despite the higher percentage of high-priority recipients in the broader sharing groups (i.e., regional and national). Another common argument is that broader organ sharing would decrease transplantation for local candidates, particularly economically disadvantaged patients (12). However,

in models for broader allocation practices in liver transplantation, previous groups found no evidence that minorities and economically disadvantaged patients are at a disadvantage in a broader allocation system (13).

In 1998, the US Department of Health and Human Services (DHHS) issued the “Final Rule” declaring that, “organs be [allocated] based on common medical criteria, not accidents of geography” (9). Subsequently, the DHHS and Institute of Medicine (IOM) assembled an expert panel to assess the impact of geography on organ allocation and waitlist outcomes in liver transplantation. The IOM panel concluded that “broader sharing of organs led to an overall increase in the rate at which the most severely ill patients were transplanted and a concomitant decrease in the excess transplantation of the least severely ill patients, without increasing pre-transplantation mortality” (1). Despite the introduction of the “Final Rule” and the findings of the IOM panel, no significant policy change has been adopted to minimize the impact of geography on the allocation of donor lungs.

The organ transplant community still follows many guidelines for donor selection and organ allocation which are based on expert opinions and are not data driven. These criteria if strictly followed lead to an overall smaller number of organs transplanted and/or inefficient distribution of organs as well as an overall suboptimal organ utilization. There is an ever increasing body of evidence promoting revisions and changes in these guidelines. Reyes et al. (14) showed that even though in more than half of lung transplant cases at least one of the donor selection guidelines was not followed, there was no difference in clinical outcome in lung transplant patients. Speicher et al. reported that among donors for single lung transplant (SLT), less than half of the cases led to use of

Iribarne et al.

the second donor lung. Independent predictors of non-utilization included ABO incompatibility and lower body surface area. The authors suggested that UNOS should consider requiring OPOs to more aggressively place both lungs for SLT including placing the other lung outside the LAS system (15). Ware et al. (16) performed an analysis of rejected donor lungs by conventional criteria and found that 41% of those organs could be utilized if prospectively defined criteria by the California Transplant Donor Network were used.

Limitations

These data have several limitations. First, large patient registries often suffer from incompleteness in data entry. Fields contained within this database, however, were well populated with a 90–99% data entry rate for the majority of variables. Patients with missing LAS data ($n = 15$) were not included in the analysis; however, given the large sample size ($n = 17\,416$), it is unlikely that these excluded patients would have significantly altered the results.

Second, the stratification of the study population by LAS into low, medium, and high-priority recipients is not based on clinical set-points. Nonetheless, the differences in clinical profiles of patients with LAS <50 , LAS 50–75, and LAS >75 are clinically meaningful, and other studies have used these thresholds, after demonstrating that waitlist mortality increases in a stepwise fashion with each 10 point increase in LAS (8).

Finally, the survival analysis by GST does not adjust for baseline differences between groups. Therefore, causal relationships between GST and post-transplant survival cannot be determined.

Implications

This analysis provides evidence that broader geographical sharing of lungs may result in an increased percentage of high-priority lung recipients. In an effort to identify mechanisms to further improve the lung allocation system and therefore increase the survival benefit from transplantation, our future research agenda includes a series of analyses intended to explore the impact of local allocation of organs on waitlist outcomes. By adapting statistical methods applied by an IOM panel assembled by the DHHS (1) to explore similar questions in liver transplantation, this proposal will use mixed-effects multinomial logistic regression analysis to test the central hypothesis that organ sharing over broader geographies would

result in better allocation of organs as measured by:

1. Higher rates of organ allocation to higher priority candidates
2. Improved survival on the waiting list among lung transplant candidates
3. Increased total net survival benefit of transplantation aggregated across all lung transplant candidates.

If findings of this analysis support the primary hypothesis, this study will provide important evidence to support changes in the lung allocation policy, namely that organs over broader geographies will increase the net survival benefit of transplantation.

Authors' contributions

Alexander Iribarne: Concept, Manuscript writing, Statistical analysis; David Meltzer: Critical revision of the paper; Joshua Sonett: Research design, interpretation of data; Dhaval Chauhan: Drafting the paper and revising it critically; Robert Gibbons: Statistical analysis, interpretation of results; Wicki Vigneswaran: Approval of final versions; Mark Russo: Research design, concept and approval of final versions.

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Distribution donor lungs geography

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